

**REMARKS**

This paper is submitted in response to the Office Action mailed August 20, 2003. Applicants also thank the Examiner and his SPE for the telephonic interview of November 6, 2003 in which certain issues were clarified.

Claims 14, 19-21, and 28 have been objected to as being dependent upon a rejected base claim, but the Examiner has indicated that these claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants have made such amendments.

Applicants have amended Claims 1, 2, 5, 7, 9, 14, 16, 18, 19, 22, 27, and 28, and added Claim 29. Applicants have also canceled Claims 12, 13, and 15 without disclaimer or prejudice to the prosecution of the subject matter of these claims in subsequent divisional or continuation patent applications. Thus, following entry of this amendment, claims 1-11, 14, and 16-29 are pending.

**I. The Objections to the Claims Should Be Withdrawn**

Claims 14, 19-21, and 28 have been objected to as being dependent upon a rejected base claim, but the Examiner has indicated that these claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

As set forth above in the Listing of Claims, Applicants have amended Claims 14, 19, and 28 so that they are in independent form, including all of the limitations of the base claim and any intervening claims. Applicants therefore respectfully request that the Examiner withdraw the objections to Claims 14, 19-21, and 28, and allow these claims.

**II. The Rejections under 35 U.S.C. § 103(a) Should Be Withdrawn**

Claims 1, 7, 8, 11-13, 15-18, and 22-27 have been rejected under 35 U.S.C. § 103(a) as being obvious in view of Kotula *et al.* (*Biotechnology* 1991;9:1386-1389) in combination with Neill *et al.* (*Gene* 1987;55:303-317). According to the Examiner, Kotula *et al.* teach a recombinant yeast cell comprising a non-yeast DNA (mouse IgK gene) wherein the codon bias of the mouse gene is optimized for the expression of the gene in the yeast *S. cerevisiae*; wherein the region of the mouse DNA having a high content of codons that are poorly suited to yeasts contains at least two poorly suited codons among ten consecutive codons; wherein the replaced codons are in the 5' region of the gene; and wherein the optimized gene is operably linked to heterologous 5' and 3' regulatory elements. Although the Examiner concedes that Kotula *et al.* do not specifically teach production of a plant protein in yeast, he asserts that the teachings of Kotula *et al.* provide a general "road map for the optimization of non-mIGK genes" for expression in yeast. The Examiner further asserts that Neill *et al.* teach expression of the plant protein α-gliadin in yeast, and that this expression is limited by availability of a specific glutamine tRNA. The Examiner then concludes that it would have been obvious to one of ordinary skill in the art to combine the teachings of Kotula *et al.* and Neill *et al.* to optimize codon utilization of a plant gene for expression in yeast to maximize expression of the plant protein.

Claims 2-6, 9, and 10 have been rejected under 35 U.S.C. § 103(a) as being obvious by the combination of Kotula *et al.* and Neill *et al.* as applied above to Claim 1 in further view of the "Codon Usage Database" (<http://www.kazusa.or.jp/codon>). The Examiner contends that, as set forth above, Kotula *et al.* teach optimization of codon utilization for enhanced production of heterologous proteins in yeasts, but do not specifically teach which codons should be employed in yeast nor the utilization frequencies of desirable or undesirable codons. The Examiner asserts, however, that one

of ordinary skill in the art could obtain such information by combining the teachings of Kotula *et al.* with those of the Codon Usage Database.

The relative positions of Applicants and the Examiner *vis a vis* the teachings of Kotula *et al.*, Neill *et al.*, and the Codon Usage Database have been set forth in the response to the previous Office Action and reiterated in part in a telephone interview held on November 6, 2003. The Examiner has maintained that one of ordinary skill in the art, reading Neill *et al.*, would have been motivated to apply the teaching of Kotula *et al.* to overcome the limitation on  $\alpha$ -gliadin protein expression in yeast, because, Neill *et al.* suggest that the observed limitation on the expression of the plant  $\alpha$ -gliadin gene in yeast is due to a "problem with codon bias usage" because "the yeast is deficient in a particular codon needed in high abundance for the production of  $\alpha$ -gliadin." The Examiner has further alleged that one of ordinary skill in the art would have been motivated to overcome the limitation in plant gene expression in yeast observed by Neill *et al.* by combining Neill *et al.* with Kotula *et al.* to maximize expression of non-yeast genes in yeasts using codon optimization.

In view of the Examiner's position regarding the teachings of Kotula *et al.* and Neill *et al.*, and in order to advance the prosecution of the instant application, Applicants herein have amended

Claim 1 to indicate that, in the claimed recombinant non-yeast DNA encoding a plant protein of interest, at least 75% of the codons that are poorly suited for expression in yeasts are replaced by synonymous codons coding for the same amino acid that are well-suited for expression in yeasts.

Applicants also have added Claim 29 to claim a recombinant non-yeast DNA encoding a plant protein of interest wherein 100% of the codons that are poorly suited for expression in yeasts are replaced by synonymous codons coding for the same amino acid that are well-suited for expression in yeasts. Applicants have amended Claim 2 to be dependent from Claim 1 or Claim 29. Applicants also have amended Claims 5, 7, 9, 16, 18, 22 and 27 so that they now depend from Claim 2 rather

than Claim 1, thereby importing the limitations of amended Claim 1 and new Claim 29 into all pending claims except those that the Examiner indicated would be allowable if rewritten into independent form including all of the limitations of the base claim and any intervening claims (Claims 14, 19-21, and 28). Support for these amendments may be found in the instant specification, for example at page 5, lines 12-15. Applicants assert that Kotula *et al.*, whether considered separately or in combination with the Codon Usage Database and/or Neill *et al.*, fail to teach or suggest replacement of more than approximately 53% of codons of a heterologous gene by yeast-preferred codons. Thus, the claims of the instant application, as presently amended, are not obvious over the cited art which does not teach or suggest, either alone or in combination, each and every element of the claims as presently amended. In light of these amendments and the foregoing discussion, Applicants respectfully request withdrawal of the rejection of Claims 1-13, 15-18, and 22-27 under 35 U.S.C. § 103(a) as being obvious in view of the combined teachings of Kotula *et al.*, Neill *et al.*, and the Codon Usage Database.

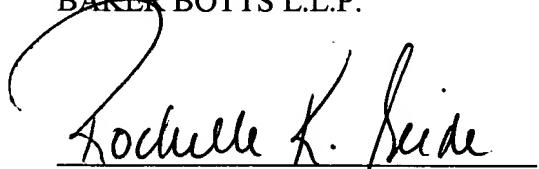
**CONCLUSION**

Based on the foregoing remarks and in light of the amendments, Applicants submit that the present application is in condition for allowance. A Notice of Allowance is therefore respectfully requested.

Applicants believe that a fee of a \$469.00 is due in connection with the filing of this amendment. This amount includes the fee of \$110.00 as required for a one-month extension of time for non-small entities under 37 C.F.R. §1.17(a)(1) and a fee of \$359.00 for additional claims. Accordingly, a check for \$469.00 is enclosed. Should any additional fees be required in connection with the filing of this Amendment, or should any overpayment have been made, the Commissioner is hereby authorized to charge and additional fees or credit any overpayments in connection with this communication to Deposit Account Number 02-4377. A duplicate copy of this communication is enclosed.

Respectfully submitted,

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Enclosures

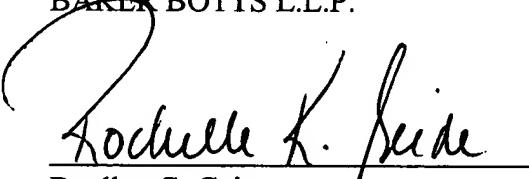
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